

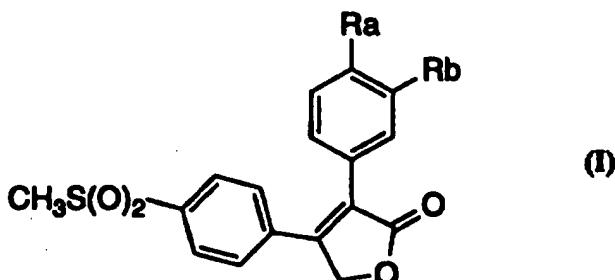
## INTERNATIONAL APPLICATION PUBLISHED UNDER

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(54) Title: PROCESS FOR MAKING PHENYL HETEROCYCLES USEFUL AS COX-2 INHIBITORS

## (57) Abstract

The invention encompasses a process for making compounds of formula (I) useful in the treatment of cyclooxygenase-2 mediated diseases.



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- 1 -

## TITLE OF THE INVENTION

### PROCESS FOR MAKING PHENYL HETEROCYCLES USEFUL AS COX-2 INHIBITORS

#### 5 BACKGROUND OF THE INVENTION

This invention concerns a process for making certain anti-inflammatory compounds. In particular, the application concerns a process for making compounds of formula I as disclosed hereinunder, which compounds are potent cyclooxygenase-2 inhibitors.

10 Non-steroidal, antiinflammatory drugs exert most of their antiinflammatory, analgesic and antipyretic activity and inhibit hormone-induced uterine contractions and certain types of cancer growth through inhibition of prostaglandin G/H synthase, also known as cyclooxygenase. Up until recently, only one form of cyclooxygenase had been characterized, this corresponding to cyclooxygenase-1 or the 15 constitutive enzyme, as originally identified in bovine seminal vesicles. Recently the gene for a second inducible form of cyclooxygenase (cyclooxygenase-2) has been cloned, sequenced and characterized from chicken, murine and human sources. This enzyme is distinct from the 20 cyclooxygenase-1 which has now also been cloned, sequenced and characterized from sheep, murine and human sources. The second form of cyclooxygenase, cyclooxygenase-2, is rapidly and readily inducible by a number of agents including mitogens, endotoxin, hormones, cytokines and growth factors. As prostaglandins have both 25 physiological and pathological roles, we have concluded that the constitutive enzyme, cyclooxygenase-1, is responsible, in large part, for endogenous basal release of prostaglandins and hence is important in their physiological functions such as the maintenance of gastrointestinal integrity and renal blood flow. In contrast, we have concluded that the 30 inducible form, cyclooxygenase-2, is mainly responsible for the pathological effects of prostaglandins where rapid induction of the enzyme would occur in response to such agents as inflammatory agents, hormones, growth factors, and cytokines. Thus, a selective inhibitor of cyclooxygenase-2 will have similar antiinflammatory, antipyretic and

- 2 -

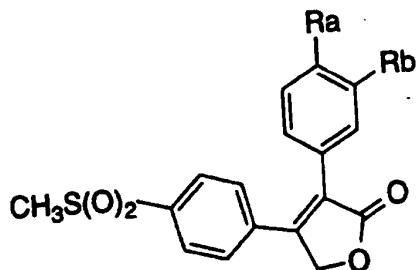
analgesic properties to a conventional non-steroidal antiinflammatory drug, and in addition would inhibit hormone-induced uterine contractions and have potential anti-cancer effects, but will have a diminished ability to induce some of the mechanism-based side effects.

5 In particular, such a compound should have a reduced potential for gastrointestinal toxicity, a reduced potential for renal side effects, a reduced effect on bleeding times and possibly a lessened ability to induce asthma attacks in aspirin-sensitive asthmatic subjects.

WO 94/ 15932 published July 21, 1994 discloses a multi-step method of making bi-aryl furans via bi-aryl lactones, which method utilizes a keto-ester internal cyclization to the lactone. We have found that a significant amount of undesired by-products are produced by use of the disclosed process scheme, due to the external cyclization reactions which compete with the desired internal cyclization. While these by-products can be removed by suitable separation and purification techniques, we have sought to identify alternative processes to obviate the difficulties.

## SUMMARY OF THE INVENTION

**20 SUMMARY OF THE INVENTION**  
The invention encompasses a process for making compounds of Formula I useful in the treatment of inflammation and other cyclooxygenase-2 mediated diseases.



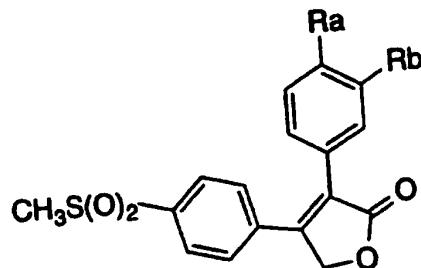
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- 3 -

DETAILED DESCRIPTION OF THE INVENTION

The invention encompasses a process for making compounds of Formula I useful in the treatment of inflammation and other cyclooxygenase-2 mediated diseases

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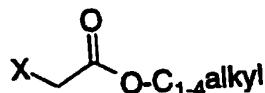
I

Ra and Rb are each independently selected from the group consisting of

10 (1) hydrogen, and  
 (2) halo, wherein halo is defined to include fluoro, bromo and chloro;

the process comprising:

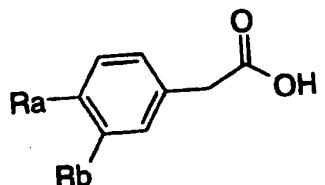
(a) reacting a compound of Formula A1



A1

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wherein X is chloride or bromo, in a non-reactive solvent and in the presence of a suitable base, with a compound of Formula A2

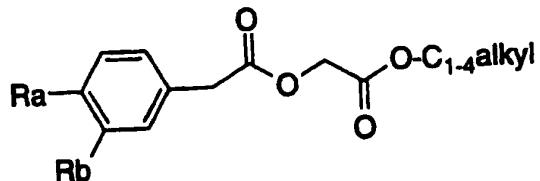


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A2

- 4 -

to yield a compound of Formula A3



A3

5 For purposes of this specification non-reactive solvents include halocarbon solvents such as mono or di-halo C<sub>1-4</sub> alkyl including dichloromethane; etheral solvents such as diethyl ether di-n-butyl and diisopropyl ethers, cyclic ethers such as tetrahydropyran, and tetrahydrofuran; aromatic solvents such as benzene, toluene and xylene; and C<sub>6-10</sub> linear, branched or cyclic hydrocarbon solvent including hexane. For this step, the non-reactive solvents are preferably acetonitrile or tetrahydrofuran. Suitable bases include but are not limited to pyrrole, pyridine, pyrrolidine, imidazole and lutidine, di C<sub>1-3</sub>alkylamine such as diisopropylamine and tri C<sub>1-3</sub>alkylamine such as triethylamine and diisopropyl ethylamine, metal amides, wherein metal is defined as sodium, potassium or lithium, including di-C<sub>1-4</sub> alkyl amides such as lithium diisopropylamide; C<sub>1-4</sub> alkyl metals such as n-butyllithium; metal C<sub>1-4</sub> alkoxides, such as 10 potassium t-butoxide; metal hydrides such as sodium or potassium hydride; and metal carbonates sodium and potassium carbonates. For this step, the suitable bases are preferably triethylamine or diisopropyl ethylamine.

15 The molar ratio of compound of Formula A1 to compound of Formula A2 may typically be varied from 1:1.5 to 1.5:1; preferably 1:1 to 1:1.2. Excess Formula A2 may be used. Similarly, the molar ratio of compound of Formula A1 to base may typically be varied from 1:1.5 to 1.5:1. Preferably the the molar ratio of Formula A1 to base is 20 1:1 to 1:1.5. The reaction step may conveniently be conducted at a temperature range of 0 to 50°C; preferably 10 to 25°C and is allowed to 25 30

- 5 -

proceed until substantially complete in from 2 to 18 hours; typically 5 to 10 hours.

5 (b) reacting a compound of Formula A3  
 5 in a polar organic solvent, in the presence of a strong base to yield a compound of Formula B1



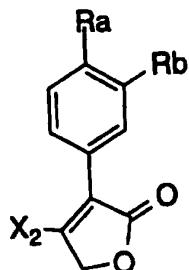
B1

10 For purposes of this specification the polar organic solvent is defined to include, but is not limited to, N,N-dimethylformamide, tert-butyl alcohol, tetrahydrofuran and dimethylsulfoxide. N,N-dimethylformamide or tert-butyl alcohol are preferred. Similarly, the strong base is defined to include, but is not limited to metal amides, 15 wherein metal is defined as sodium, potassium or lithium, including di-C1-4 alkyl amides such as lithium diisopropylamide; metal C1-4 alkoxides, such as potassium t-butoxide and metal hydrides such as sodium or potassium hydride. Tert-butoxide (such as potassium tert-butoxide) or 1,8-diazabicyclo[5.4.0]undec-7-ene are preferred.

20 Typically, molar ratio of compound of Formula A3 to strong base is preferably approximately 1:1 but may vary in either direction by 10%. The reaction step may be conducted at a temperature range of 25 to 80°C; preferably 70°C, and is allowed to proceed until substantially complete in from 30 minutes to 5 hours; typically 45 25 minutes to 1 hour.

- 6 -

(c) reacting a compound of Formula B1 in a non-reactive solvent (as defined above), with an activating agent to yield a compound of Formula C1



C1

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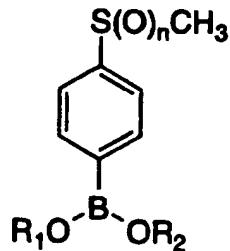
wherein X2 is a good leaving group;

For purposes of this specification the activating agent is defined to include, but is not limited to PBr3; PCl5; POCl3; (PhO)2P(O)Cl; MeSO2Cl; 4-MePhSO2Cl in the presence of a tri-C1-4alkylamine, such as triethylamine; and (CF3SO2)2O; (FSO2)2O in the presence of a tri-C1-4alkylamine, such as triethylamine. Accordingly, X2 is defined to include, but is not limited to fluorosulfonate, mesylate, tosylate, Br, Cl, OP(O)(PhO)2 and OSO2CF3. That is, the activating agent is selected to incorporate one of the desired leaving groups into the compound of Formula C1. In this step the non-reactive solvent is preferably dichloromethane, acetonitrile or tetrahydrofuran.

Typically the molar ratio of compound of Formula B1 to compound of activating agent may conveniently be varied from approximately 1.2:1 to 1:1.2, but additional activating agent may be used. Similarly, the molar ratio of compound of Formula B1 to base may conveniently be varied from 1:1 to 1:1.5; preferably 1:1.2. The reaction step may be conducted at a temperature range of -10 to 50°C; preferably 0 to 25°C and is allowed to proceed until substantially complete in from 5 minutes to 5 hours; typically 30 minutes to 2 hours.

(d) coupling a compound of Formula C1 with a compound of Formula D2

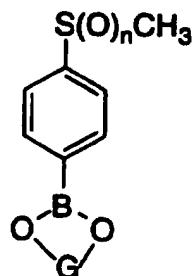
- 7 -



D2

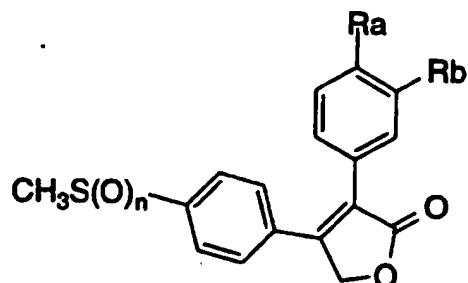
wherein n is 0, 1 or 2;

5 R<sub>1</sub> and R<sub>2</sub> are each independently selected from H or C<sub>1-4</sub>alkyl or R<sub>1</sub> and R<sub>2</sub> are joined, such that together with the atoms to which they are attached there is formed the compound of the formula



wherein G is a saturated or unsaturated monocyclic carbon ring of 5, 6 or 7 atoms,

10 the coupling step being conducted in a coupling solvent in the presence of a coupling base and a transition metal catalyst to yield a compound of Formula D3



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D3

- 8 -

and where n is 0 or 1, oxidizing the compound of Formula D3 to a compound of Formula I.

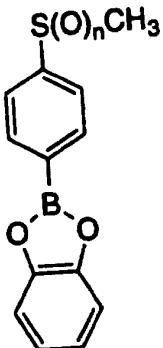
For purposes of this specification coupling bases include 5 but are not limited to metal hydroxides including barium, potassium, sodium, or lithium, thallium hydroxides; metal C1-4 alkoxide such as sodium, potassium or lithium t-butoxide; and metal carbonate such as potassium or sodium carbonates. The coupling solvent is defined to include di-C1-3alkyl formamide such as dimethyl formamide, di-10 C1-3alkyl sulfoxide such as dimethylsulfoxide, N-methylpyrrolidinone, N-ethylpyrrolidinone and sulfolane as well as halocarbon solvents such solvents as mono or di-halo C1-4 alkyl including dichloromethane; etheral solvents such as diethyl ether di-n-butyl and diisopropyl ethers, cyclic ethers such as tetrahydropyran, and tetrahydrofuran; aromatic 15 solvents such as benzene, toluene and xylene; and C6-10 linear, branched or cyclic hydrocarbon solvent including hexane.

For purposes of this specification transition metal catalyst is defined to include Pd<sup>0</sup> catalysts including Pd (dba)2, Pd2 (dba)3, Pd2 (dba)3·CHCl3 wherein dba is defined as dibenzylidineacetone and 20 Pd(triphenylphosphorous)4. As appreciated by those of skill in the art, other standard coordinating ligands may also be used. PdII catalysts may also be employed including Pd(OAc)2 and PdCl2. Nickel catalysts may also be used.

Typically the molar ratio of compound of Formula C1 to 25 compound of D2 may conveniently be varied from 1.5:1 to 1:1.5; preferably 1:1.2. Excess D2 may be used. Similarly, the ratio of compound of Formula C1 to transition metal catalyst is typically 1:0.02 to 1:0.10; preferably about 1:0.05. The reaction step a may be conducted at a temperature range of 30 to 80°C; preferably 57 to 62°C, 30 and is allowed to proceed until substantially complete in from 2 to 20 hours; typically 4 to 5 hours.

Illustrative of the compound of formula D2 when R1 and R2 are joined is:

- 9 -



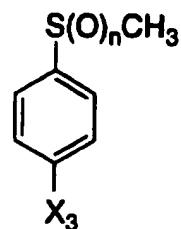
The oxidation may be accomplished by a number of means available in the art. See, for example Can. J. Chem. 59, 720 (1981),  
 5 Can. J. Chem. 60, 618 (1982), J. Chem. Soc. (C) 1969, 233, J. Org. Chem., 28, 1140 (1963), Org. Prep. Proceed. Int. 13, 137 (1981), L. Org. Chem., 50, 1544, (1985), Chem. Ber., 119, 269, (1986), and Synthesis, 1015, 1987. We have found oxidation with oxone in a two phase solvent to be surprisingly superior in that undesired side-reaction 10 oxidations are minimized. In this step 2 to 5 equivalents or more of oxidant per mole of compound of Formula D3 may be used. The two phase solvents include but are not limited to methanol in water, methylene chloride in water, and toluene in water. In addition, when a two phase solvent system is used, a phase transfer catalyst such as a tetra 15 C1-4alkylammonium halide or other salt, (such tetra-n-butylammonium salts, Aliquat 336, Triton B) or polyethylglycol reagents (such as TWEEN 40) may be added to the reaction mix (0 to 5% of total volume). The reaction step a may conveniently be conducted at a temperature range of 10 to 35°C; preferably 25°C, and is allowed to 20 proceed until substantially complete in from 5 to 15 hours; typically 4 to 5 hours.

Preferably, Ra and Rb are each independently hydrogen or fluoro. Other choices are disclosed in Table 1.

Most preferable compounds of Formula I are  
 25 3-(3,4-Difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone, and  
 3-phenyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone.

- 10 -

The reagent compound of Formula D2 is prepared by reacting a compound of Formula E1



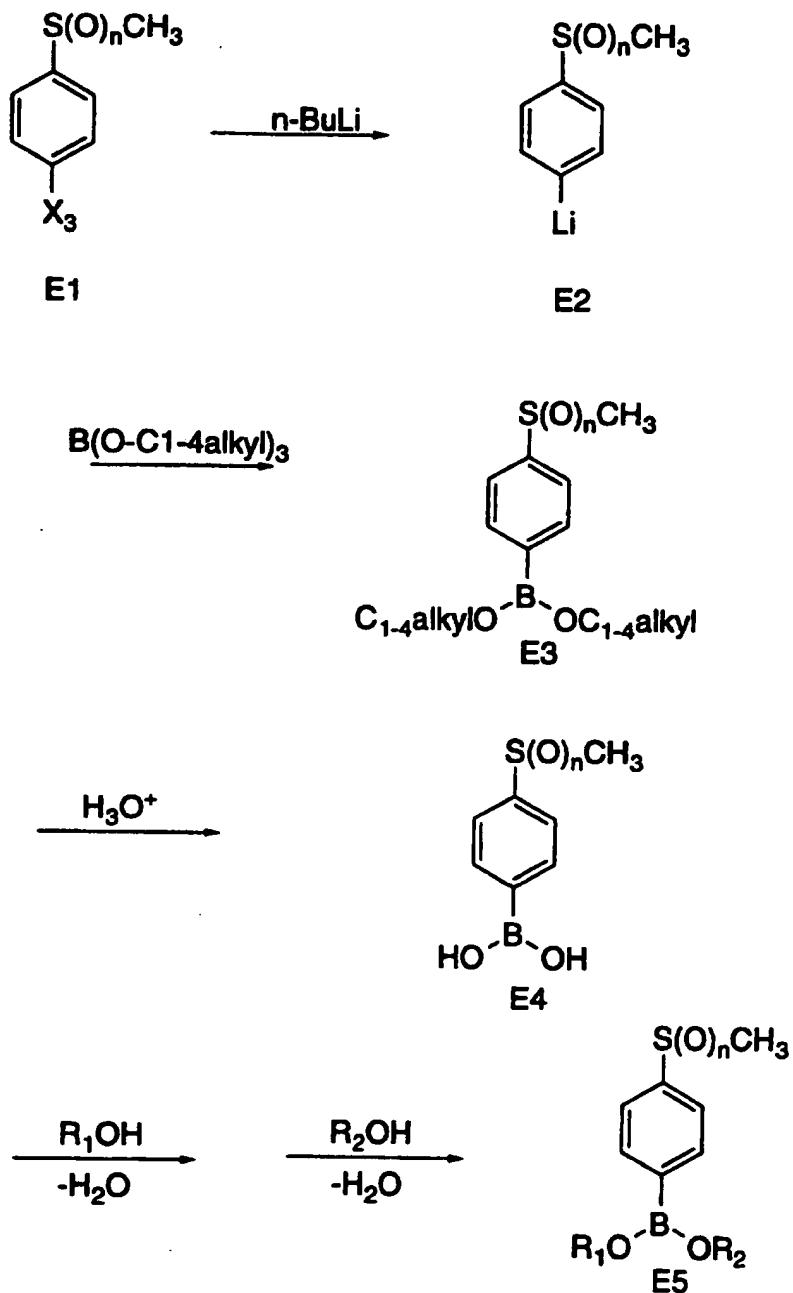
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E1

wherein  $X_3$  is chloro or bromo,  
in a non-reactive solvent (as defined above) with C<sub>1-4</sub>alkyllithium to yield a compound of Formula D2, as shown in the following scheme:

- 11 -

## SCHEME I



5 In overview, E1 undergoes metallation with n-butyl lithium; is then boronated, for example with  $\text{B}(\text{O-i-propyl})_3$ ; and is then acidified to form E4. Further reaction with  $\text{R}_1\text{OH}$  and  $\text{R}_2\text{OH}$  wherein

- 12 -

R<sub>1</sub> and R<sub>2</sub> are defined as above provides the intermediate boronic esters.

The Compound of Formula I is useful for the relief of pain, fever and inflammation of a variety of conditions including

5      rheumatic fever, symptoms associated with influenza or other viral infections, common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis degenerative joint diseases (osteoarthritis), gout and ankylosing spondylitis, bursitis, burns,

10     injuries, following surgical and dental procedures. In addition, such a compound may inhibit cellular neoplastic transformations and metastatic tumor growth and hence can be used in the treatment of cancer. Compounds of formula I may also be useful for the treatment of dementia including pre-senile and senile dementia, and in particular,

15     dementia associated with Alzheimer Disease (ie Alzheimer's dementia).

By virtue of its high cyclooxygenase-2 (COX-2) activity and/or its selectivity for cyclooxygenase-2 over cyclooxygenase-1 (COX-1) as defined above, compounds of formula I will prove useful as an alternative to conventional non-steroidal antiinflammatory drugs

20     (NSAID'S) particularly where such non-steroidal antiinflammatory drugs may be contra-indicated such as in patients with peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis or with a recurrent history of gastrointestinal lesions; GI bleeding, coagulation disorders including anemia such as hypoprothrombinemia, haemophilia or other bleeding problems (including those relating to reduced or impaired platelet function); kidney disease (eg impaired renal function); those prior to surgery or taking anticoagulants; and those susceptible to NSAID induced asthma.

Compounds of the present invention are inhibitors of

30     cyclooxygenase-2 and are thereby useful in the treatment of cyclooxygenase-2 mediated diseases as enumerated above. This activity is illustrated by their ability to selectively inhibit cyclooxygenase-2 over cyclooxygenase-1. Accordingly, in one assay, the ability of the compounds of this invention to treat cyclooxygenase mediated diseases

- 13 -

can be demonstrated by measuring the amount of prostaglandin E2 (PGE2) synthesized in the presence of arachidonic acid, cyclooxygenase-1 or cyclooxygenase-2 and a compound of formula I. The IC50 values represent the concentration of inhibitor required to 5 return PGE2 synthesis to 50 % of that obtained as compared to the uninhibited control. Illustrating this aspect, we have found that the Compounds of the Examples are more than 100 times more effective in inhibiting COX-2 than they are at inhibiting COX-1. In addition they all have a COX-2 IC50 of 1 nM to 1  $\mu$ M. By way of comparison, 10 Ibuprofen has an IC50 for COX-2 of 1  $\mu$ M, and Indomethacin has an IC50 for COX-2 of approximately 100 nM.

For the treatment of any of these cyclooxygenase mediated diseases, compounds of formula I may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations 15 containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle sheep, dogs, cats, etc., 20 the compound of the invention is effective in the treatment of humans.

As indicated above, pharmaceutical compositions for treating cyclooxygenase-2 mediated diseases as defined may optionally include one or more ingredients as listed above.

The pharmaceutical compositions containing the active 25 ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical 30 compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically

- 14 -

acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the technique described in the U.S. Patent 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredients is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethyl-cellulose, methylcellulose, hydroxypropylmethycellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylene-oxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for

- 15 -

example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

5 Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, 10 hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

15 Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, 20 flavoring and coloring agents, may also be present.

25 The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain 30 sweetening and flavouring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may

- 16 -

be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also 5 be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or 10 suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Compounds of formula I may also be administered in the form of a suppositories for rectal administration of the drug. These 15 compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, jellies, solutions or 20 suspensions, etc., containing the compound of Formula I are employed. (For purposes of this application, topical application shall include mouth washes and gargles.)

Dosage levels of the order of from about 0.01 mg to about 25 140 mg/kg of body weight per day are useful in the treatment of the above-indicated conditions, or alternatively about 0.5 mg to about 7 g per patient per day. For example, inflammation may be effectively treated by the administration of from about 0.01 to 50 mg of the compound per kilogram of body weight per day, or alternatively about 30 0.5 mg to about 3.5 g per patient per day.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral

- 17 -

administration of humans may contain from 0.5 mg to 5 g of active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Dosage unit forms will generally contain between 5 from about 1 mg to about 500 mg of an active ingredient, typically 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 800 mg, or 1000 mg.

Assays for Determining Biological Activity  
10 Representative Rat Paw Edema Assay – Protocol

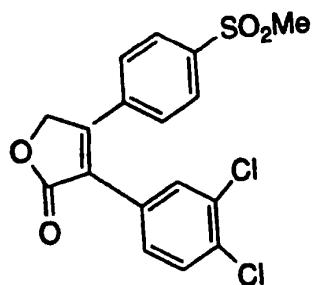
Male Sprague-Dawley rats (150-200g) were fasted overnight and were given po either vehicle (5% tween 80 or 1% methocel) or a test compound at 9 - 10 am. One hr later, a line was 15 drawn using a permanent marker at the level above the ankle in one hind paw to define the area of the paw to be monitored. The paw volume ( $V_{0h}$ ) was measured using a plethysmometer (Ugo-Basile, Italy) based on the principle of water displacement. The animals were then injected subplantarly with 50 ul of a 1% carrageenan solution in saline 20 (FMC Corp, Maine) into the paw using an insulin syringe with a 25-gauge needle (i.e. 500 ug carrageenan per paw). Three hr later, the paw volume ( $V_{3h}$ ) was measured and the increases in paw volume ( $V_{3h} - V_{0h}$ ) were calculated. The animals were euthanized by CO<sub>2</sub> 25 aphyxiation and the absence or presence of stomach lesions scored. Stomach scores were expressed as the sum of total lesions in mm. Paw edema data were compared with the vehicle-control group and percent inhibition calculated taking the values in the control group as 100%. Since a maximum of 60 - 70% inhibition (paw edema) was obtained with standard NSAIDs, ED<sub>30</sub> values were used for comparison. All 30 treatment groups were coded to eliminate observer bias. With this protocol, the ED<sub>30</sub> for Indomethacin is 1.0 mg/kg. Representative results are shown in Table I.

- 18 -

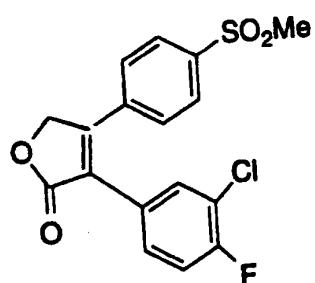
TABLE I

|       | STRUCTURE |
|-------|-----------|
| 0.35  |           |
| 0.38  |           |
| ~1.00 |           |

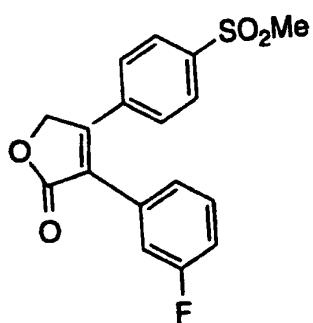
- 19 -

0.22  
0.23

0.43

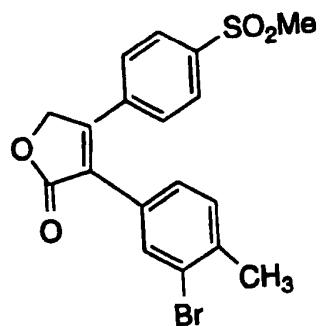


0.33

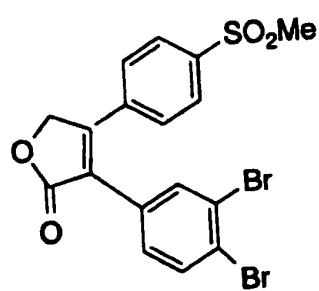


- 20 -

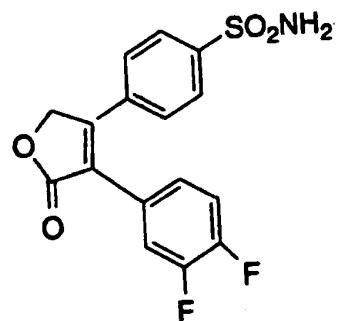
0.46



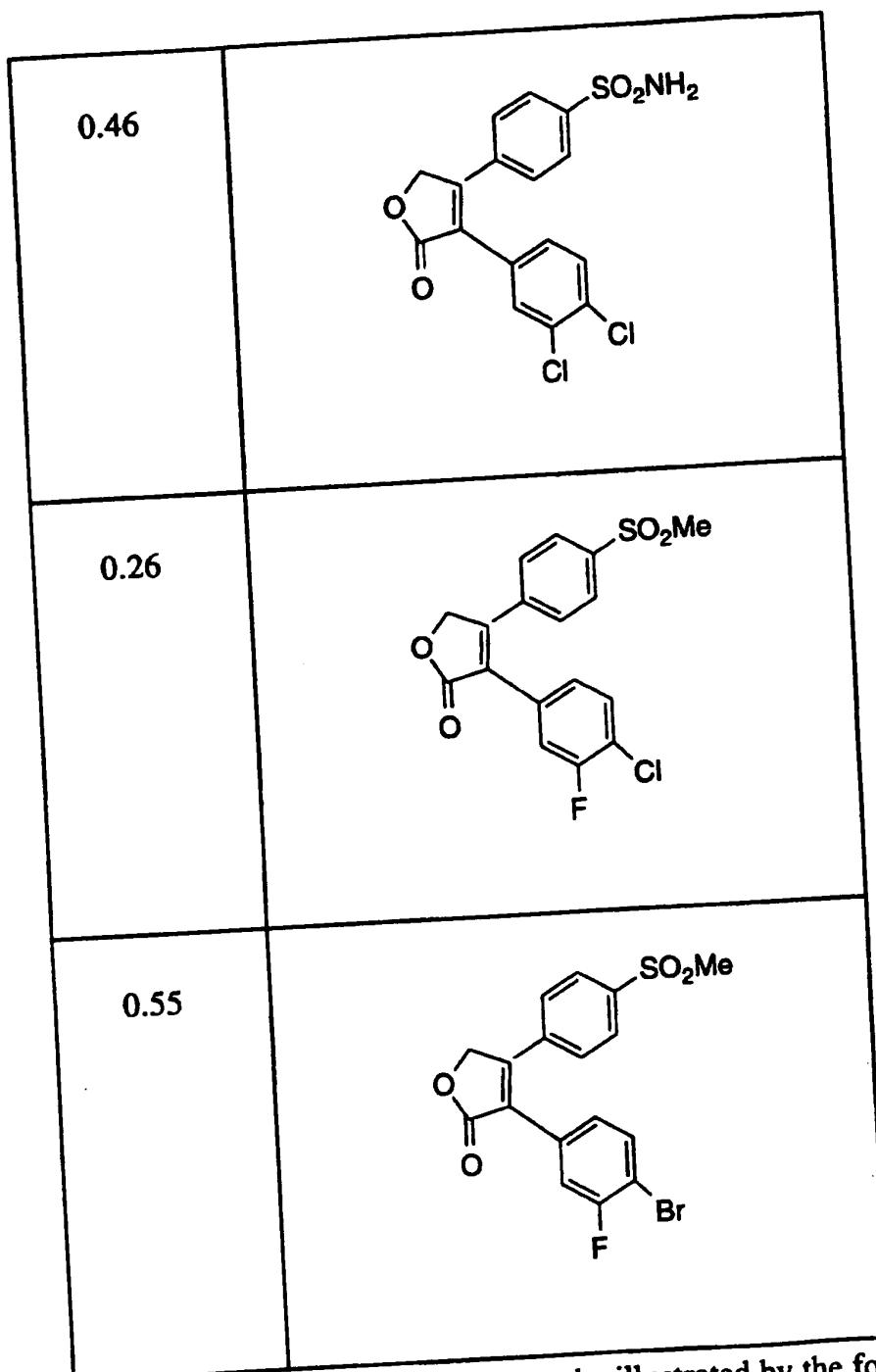
0.76



0.48



- 21 -



The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

- 22 -

(i) all operations were carried out at room or ambient temperature, that is, at a temperature in the range 18-25°C; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 pascals: 4.5-30 mm. Hg) with a bath temperature of 5 up to 60°C; the course of reactions was followed by thin layer chromatography (TLC) or High Pressure Liquid Chromatography (HPLC) and reaction times are given for illustration only; melting points are uncorrected and 'd' indicates decomposition; the melting points given are those obtained for the materials prepared as described; 10 polymorphism may result in isolation of materials with different melting points in some preparations; the structure and purity of all final products were assured by at least one of the following techniques: TLC, mass spectrometry, nuclear magnetic resonance (NMR) spectrometry or microanalytical data; yields are given for illustration only; when given, 15 NMR data is in the form of delta ( $\delta$ ) values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard, determined at 300 MHz or 400 MHz using the indicated solvent; conventional abbreviations used for signal shape are: s. singlet; d. doublet; t. triplet; m. multiplet; br. broad; etc.: in 20 addition "Ar" signifies an aromatic signal; chemical symbols have their usual meanings; the following abbreviations have also been used v (volume), w (weight), b.p. (boiling point), m.p. (melting point), L (liter(s)), mL (milliliters), g (gram(s)), mg (milligrams(s)), mol (moles), mmol (millimoles), eq (equivalent(s)).

25

The following abbreviations have the indicated meanings:

|                   |   |  |
|-------------------|---|--|
| Ac                | = | acetyl                                       |
| Bn                | = | benzyl                                       |
| DBU               | = | 1,8-diazabicyclo[5.4.0]undec-7-ene           |
| DMF               | = | N,N-dimethylformamide                        |
| Et <sub>3</sub> N | = | triethylamine                                |
| LDA               | = | lithium diisopropylamide                     |
| Ms                | = | methanesulfonyl = mesyl = SO <sub>2</sub> Me |
| MsO               | = | methanesulfonate = mesylate                  |

- 23 -

|                  |   |   |
|------------------|---|---|
| NSAID            | = | non-steroidal anti-inflammatory drug                                  |
| OXONE®           | = | 2KHSO <sub>5</sub> •KHSO <sub>4</sub> •K <sub>2</sub> SO <sub>4</sub> |
| Ph               | = | phenyl  |
| r.t.             | = | room temperature  |
| rac.             | = | racemic   |
| THF              | = | tetrahydrofuran   |
| TLC              | = | thin layer chromatography   |
| Pd(triphenyl-P)4 | = | Pd(triphenylphosphorous)4   |

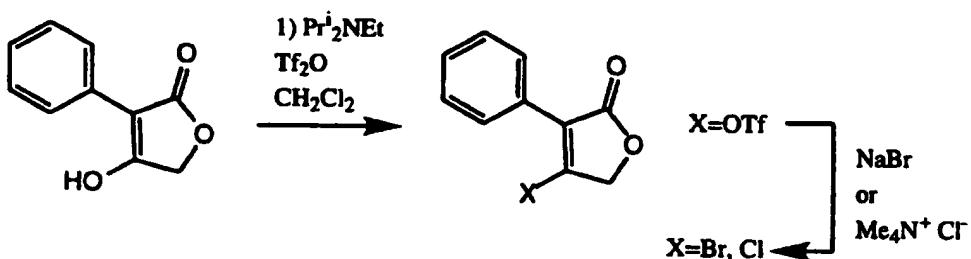
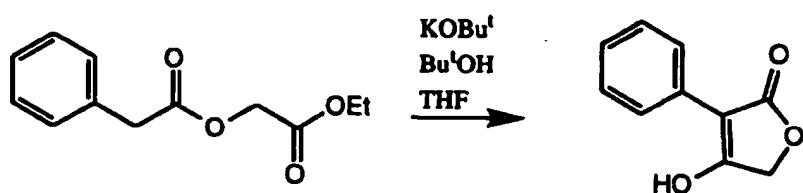
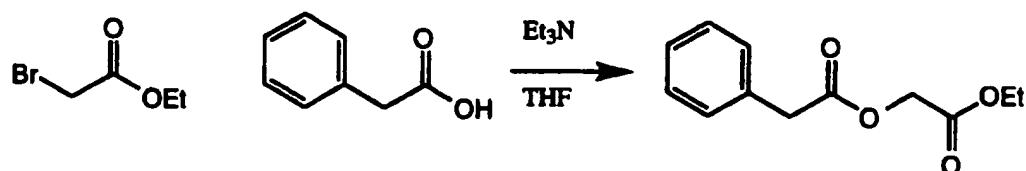
Alkyl Group Abbreviations

|       |   |                 |
|-------|---|-----------------|
| Me    | = | methyl          |
| Et    | = | ethyl           |
| n-Pr  | = | normal propyl   |
| i-Pr  | = | isopropyl       |
| n-Bu  | = | normal butyl    |
| i-Bu  | = | isobutyl        |
| s-Bu  | = | secondary butyl |
| t-Bu  | = | tertiary butyl  |
| c-Pr  | = | cyclopropyl     |
| c-Bu  | = | cyclobutyl      |
| c-Pen | = | cyclopentyl     |
| c-Hex | = | cyclohexyl      |

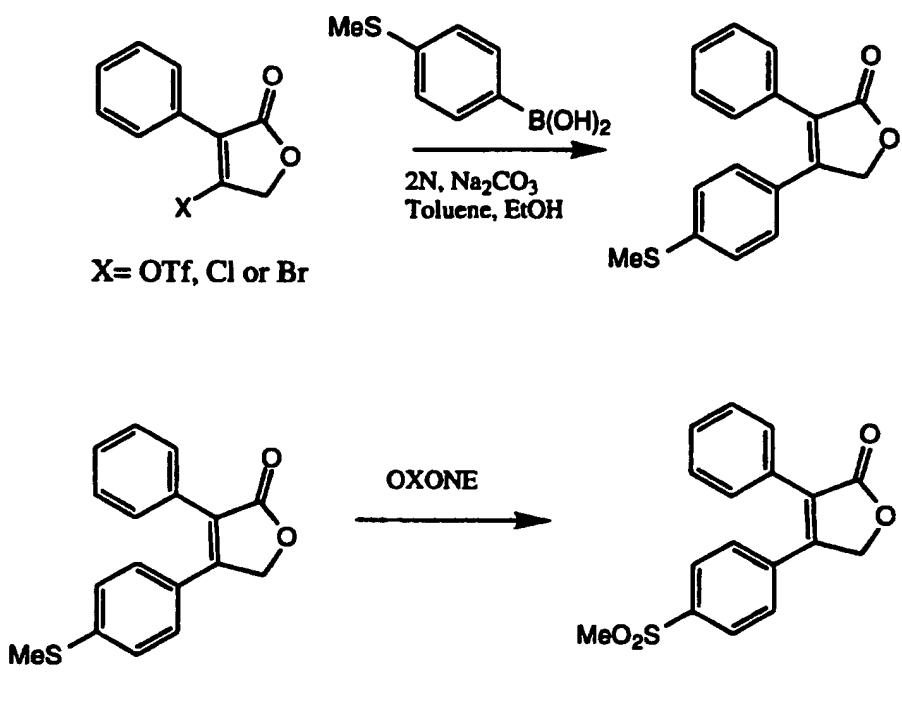
- 24 -

EXAMPLE 1

3-phenyl-4-(4-methylsulfonyl)phenyl-2(5H)-furanone.

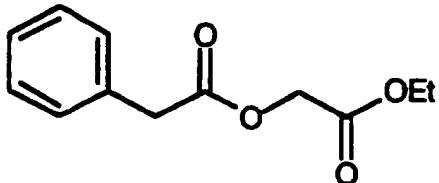


- 25 -



**Step A Preparation of the ester**

5



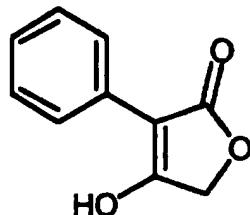
To a stirred solution of phenylacetic acid (100 g, 1 equiv) and ethyl bromoacetate (77.4 mL, 0.95 equiv.) in THF (1000 mL) was added 10 triethylamine (107.5 mL, 1.05 equiv.), and the resulting mixture was heated to 60°C for 1 h (nitrogen atmosphere). The mixture was cooled to 25°C and was then poured into a stirred mixture of ethyl acetate (1000 mL) and water (1000 mL). The layers were separated, the aq. layer was extracted with ethyl acetate (600 mL) and the combined 15 organic extracts were washed with sat. sodium bicarbonate solution (500 mL) and with brine (300 mL). The solvent was removed under reduced pressure to give the ester (145 g, 94%).  $^1\text{H}$  nmr, 300 MHz,  $\text{CDCl}_3$ ),

- 26 -

1.25 (3H, t, J=7 Hz), 3.75 (2H, s), 4.20 (2H, q, J=7 Hz), 4.60 (2H, s), 7.2-7.4 (5H, m).

**Step B Preparation of the tетronic acid**

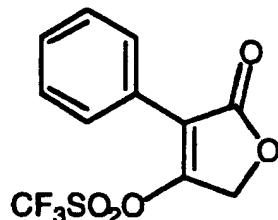
5



To a stirred solution of potassium tert-butoxide (10 g, 1 equiv.) in tert-butanol (80 mL) at 25°C (nitrogen atmosphere) was added the ester

10 (10g, 1 equiv.). The mixture was heated to 70°C for 60 min and then water (100 mL) and methyl tert-butyl ether (100 mL) were added. The layers were separated and the organic layer extracted with H<sub>2</sub>O (50 mL). The combined aqueous extracts were washed with methyl tert-butyl ether (50 mL) and were then acidified to pH 4 with 2N aqueous HCl. The white precipitate thus obtained was filtered and dried by suction to give the tетronic acid (5.65 g, 72%). <sup>1</sup>H nmr (300 MHz, DMSO), 4.75 (s, 2H), 7.22 (1H, t, J=8 Hz), 7.45 (2H, t, J=8 Hz), 7.9 (2H, d, J=8 Hz).

20 **Step C Preparation of triflate**



To a cold (0°C), stirred solution of the tетronic acid (680 mg, 1 equiv.) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added N,N-diisopropylethylamine (0.74 mL,

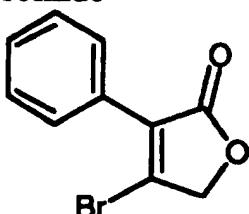
25 1.1 equiv.) followed by trifluoromethanesulfonyl anhydride (0.65 mL, 1 equiv) (nitrogen atmosphere). The solution was stirred for 10 min at 0°C and was then poured into a stirred mixture of H<sub>2</sub>O (10 mL) and

- 27 -

ethyl acetate (20 mL). The layers were separated and the organic layer was washed with 1N HCl (10 mL) and then with water (10 mL). The solvent was removed to give the triflate as a yellow oil (which solidified upon storage at -10°C).  $^1\text{H}$  nmr (300 MHz,  $\text{CDCl}_3$ ) 5.08 (2H, s), 7.4-

5 7.5 (3H, m), 7.7-7.8 (2H, m).

**Step D Preparation of the bromide**



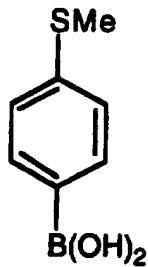
10

A mixture of the triflate (15.3 g, 1 equiv) and lithium bromide (25 g, 5 equiv) in acetone (100 mL) was heated at 50 °C for 30 min (nitrogen atmosphere). The mixture was cooled to 25°C and was then partitioned between ethyl acetate (200 mL) and  $\text{H}_2\text{O}$  (100 mL). The aqueous layer

15 was extracted with ethyl acetate (50 mL) and the combined organic extracts were washed with brine (50 mL) and were then concentrated to give the bromide (11.28 g, 90%).  $^1\text{H}$  nmr (300 MHz,  $\text{CDCl}_3$ ), 4.85 (2H, s), 7.4-7.5 (3H, m), 7.7-7.8 (2H, m).

20

**Step E Preparation of 4-methylthio-phenylboric acid**



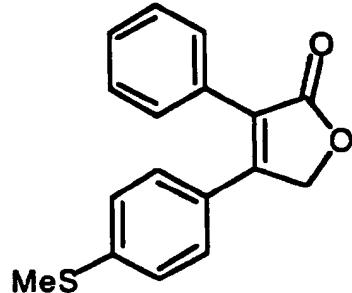
25 To a cold (-75 to -78°C), stirred solution of 4-bromothioanisole (20 g, 1 equiv.) and triisopropyl borate (33 mL, 1.45 equiv.) in dry THF (350

- 28 -

mL) was slowly added a solution of n-butyllithium (1.5 M in hexanes) over 3 h (nitrogen atmosphere). The resulting mixture was then stirred at -78°C for 30 min and then was allowed to warm to 25°C over 1 h. Aqueous sulfuric acid (2 M, 200 mL) was added slowly (internal 5 temperature rose to 30°C during addition) and the mixture was stirred at 25 °C for 2 h. The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 100 mL). The combined organic extracts were then concentrated to approx. 30 mL and to the resulting 10 slurry was added water (100 mL). The mixture was stirred for 10 h, and the solid was filtered and was washed with toluene and dried by suction, to give the boronic acid (15.9 g, 95%). 1H nmr (300 MHz, DMSO), 2.5 (3H, s), 7.18 (2H, d, J=8 Hz), 7.70 (2H, d, J=8 Hz), 7.95 (2H, br s).

15

Step F Preparation of 3-phenyl-4-(methylthio)phenyl-2-(5H)-furanone via the triflate.



20 To a solution of the triflate (465 mg, 1 equiv.), Pd(tri-phenyl-P)4 (87 mg, 0.05 equiv.) in degassed toluene (3 mL) (nitrogen atmosphere) was added aq sodium carbonate (2.1 equiv, 1.6 mL of a 2M solution) and the stirred mixture was heated to 60°C. A solution of the boronic acid (304 mg, 1.2 equiv.) in ethanol (1.6 mL) was added in one batch and the 25 resulting mixture was heated at 60°C for 2 h. The mixture was cooled to 25°C and was then partitioned between ethyl acetate (10 mL) and water (5 mL). The organic layer was then concentrated to give a crude oil which was chromatographed on silica gel (30% EtOAc-70% hexanes) to give the furanone (317 mg, 70%). 1H nmr (300 MHz,

- 29 -

CDCl<sub>3</sub>), 2.5 (3H, s), 5.17 (2H, s), 7.16 (2H, d, J=8 Hz), 7.23 (2H, d, J=8 Hz), 7.35-7.45 (5H, m).

5 Preparation of 3-phenyl-4-(methylthio)phenyl-2-(5H)-furanone via the bromide.

10 To a solution of the bromide (234 mg, 1 equiv.), Pd(PPh<sub>3</sub>)<sub>4</sub> (55 mg, 0.05 equiv.) in degassed toluene (2 mL) (nitrogen atmosphere) was added aq sodium carbonate (2.1 equiv, 1.0 mL of a 2M solution) and water (1 mL) and the stirred mixture was heated to 60°C. A solution of the boronic acid (198 mg, 1.2 equiv.) in ethanol (0.75 mL) was added in one batch and the resulting mixture was heated at 60°C for 9 h. The mixture was cooled to 25°C and was then partitioned between ethyl acetate (10 mL) and water (5 mL). The organic layer was then concentrated to give a crude oil which was chromatographed on silica gel (30% EtOAc-70% hexanes) to give the furanone (265 mg, 90%).

15 Step G. Preparation of 3-phenyl-4-(4-methylsulfonyl)phenyl-2(5H)-furanone

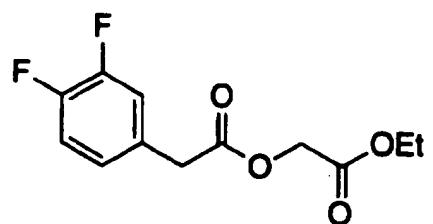
20 The sulfide (1g) and tetrabutylammonium bromide (0.034g) were dissolved in methylene chloride(15ml) at 25°C . Water (25ml) and oxone (2.7g) were added and the temperature was maintained at 25-30°C for 24h. The layers were separated and the organic layer was washed with water (20ml). The organic was concentrated to dryness in vacuo to afford the desired sulphone (0.9g).

#### EXAMPLE 2

30 3-(3,4-Difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

The title compound is prepared as described in Example 1, by substitution of the 3,4-di-fluoro ester:

- 30 -

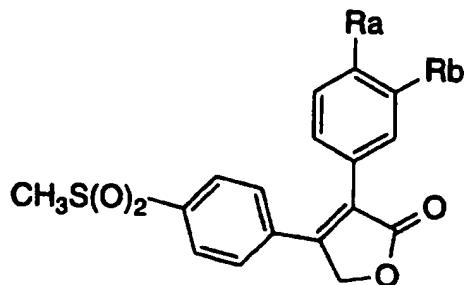


for that described in Example 1, Step A.

- 31 -

WHAT IS CLAIMED

1. A process for making compounds of Formula I



5

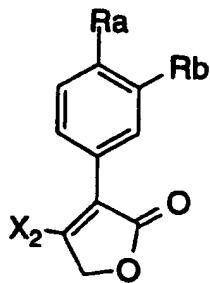
I

Ra and Rb are each independently selected from the group consisting of

- (1) hydrogen, and
- (2) halo;

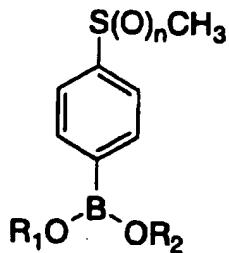
the process comprising:

10 coupling a compound of Formula C1



C1

with a compound of Formula D2



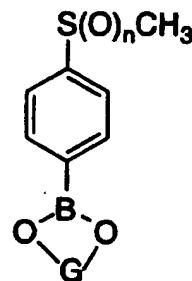
15

D2

wherein n is 0, 1 or 2;

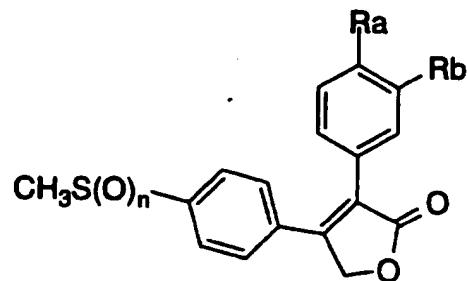
- 32 -

R<sub>1</sub> and R<sub>2</sub> are each independently selected from H or C<sub>1</sub>-4alkyl or R<sub>1</sub> and R<sub>2</sub> are joined, such that together with the atoms to which they are attached there is formed the compound of the formula



5 whererin G is a mono-cyclic saturated or unsaturated carbon ring of 5, 6 or 7 atoms,  
 the coupling step being conducted in a coupling solvent in the presence of a coupling base and a transition metal catalyst to yield a compound of Formula D3

10



D3

and where n is 0 or 1, oxidizing the compound of Formula D3 to a compound of Formula I.

15

2. A process according to Claim 1 wherein the coupling solvent is toluene or diethoxymethane; the coupling base is potassium carbonate or sodium carbonate; and the transition metal catalyst is Pd(triphenyl-P)<sub>4</sub>.

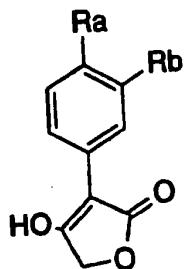
20

3. A process of claim 2 wherein

- 33 -

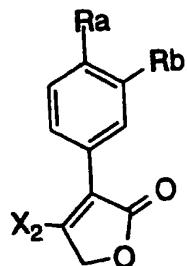
wherein n is 0;  
 R<sub>1</sub> and R<sub>2</sub> are each independently selected from H or C1-4alkyl, and  
 the coupling is conducted at 55 to 62°C.

5        4. A process according to claim 1 comprising the steps of  
           reacting a compound of Formula B1



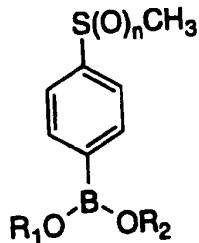
B1

in a non-reactive solvent, with an activating agent to yield a compound  
 10      of Formula C1



C1

wherein X<sub>2</sub> is a good leaving group; and  
 coupling a compound of Formula C1 with a compound of  
 15      Formula D2

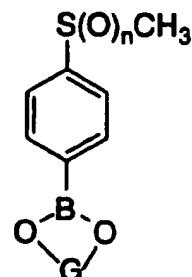


- 34 -

D2

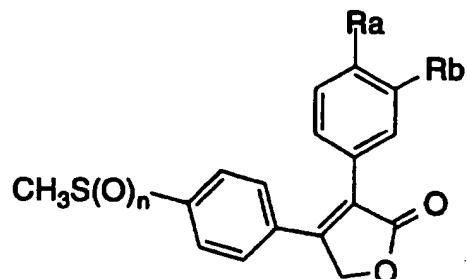
wherein n is 0, 1 or 2;

R<sub>1</sub> and R<sub>2</sub> are each independently selected from H or C<sub>1</sub>-4alkyl or R<sub>1</sub> and R<sub>2</sub> are joined, such that together with the atoms to which they are attached there is formed the compound of the formula



wherein G is a mono-cyclic saturated or unsaturated carbon ring of 5, 6 or 7 atoms,

the coupling step being conducted in a coupling solvent in the presence of a coupling base and a transition metal catalyst to yield a compound of Formula D3



D3

15 and where n is 0 or 1, oxidizing the compound of Formula D3 to a compound of Formula I.

5. A process of claim 4 wherein the coupling solvent is toluene or diethoxymethane; the coupling base is potassium carbonate or sodium carbonate; the transition metal catalyst is Pd(triphenyl-P)<sub>4</sub>; the non-reactive solvent is acetonitrile or tetrahydrofuran, and the

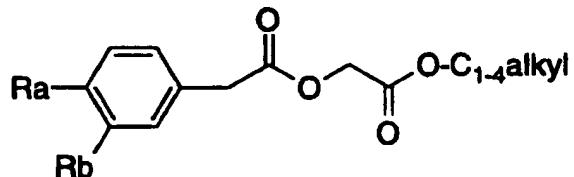
- 35 -

activating agent is  $\text{PBr}_3$  or  $\text{PCl}_5$  or  $\text{POCl}_3$  or  $(\text{PhO})_2\text{P}(\text{O})\text{Cl}$  or  $\text{MeSO}_2\text{Cl}$  or 4-MePh $\text{SO}_2\text{Cl}$  in the presence of a tri- $\text{C}_1\text{-4alkylamine}$  or  $(\text{CF}_3\text{SO}_2)_2\text{O}$  or  $(\text{FSO}_2)_2\text{O}$  in the presence of a tri $\text{C}_1\text{-4alkylamine}$ .

5                   6. A process of claim 4 wherein n is 0;  
 $\text{X}_2$  is chloro or bromo;  
 $\text{R}_1$  and  $\text{R}_2$  are each independently selected from H or  $\text{C}_1\text{-4alkyl}$ ,  
 the coupling is conducted at 55 to 62°C, and the reacting of compound  
 B1 with activating agent is conducted at 0 to 25°C.

10

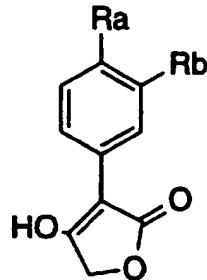
7. A process according to claim 4 comprising the steps of  
 reacting a compound of Formula A3



A3

15

in a polar organic solvent, in the presence of a strong base to yield a compound of Formula B1

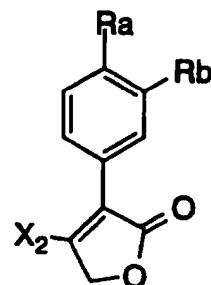


B1

20

reacting a compound of Formula B1 in a non-reactive solvent, with an activating agent to yield a compound of Formula C1

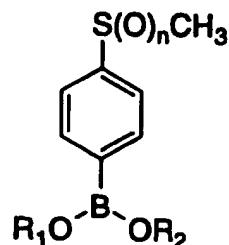
- 36 -



C1

wherein X2 is a good leaving group; and

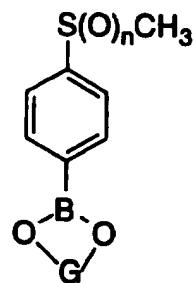
5 coupling a compound of Formula C1 with a compound of  
Formula D2



D2

wherein n is 0, 1 or 2;

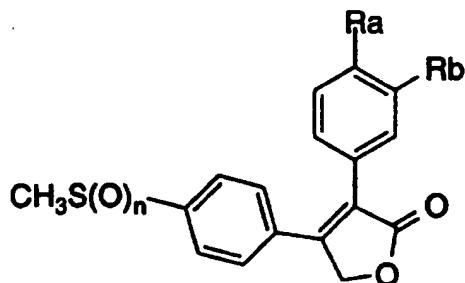
10 R1 and R2 are each independently selected from H or C1-4alkyl or R1 and R2 are joined, such that together with the atoms to which they are attached there is formed the compound of the formula



wherein G is a mono-cyclic saturated or unsaturated carbon ring of 5, 6 or 7 atoms,

- 37 -

the coupling step being conducted in a coupling solvent in the presence of a coupling base and a transition metal catalyst to yield a compound of Formula D3



5

D3

and where n is 0 or 1, oxidizing the compound of Formula D3 to a compound of Formula I.

10        8. A process of claim 7 wherein the coupling solvent is toluene or diethoxymethane; the coupling base is potassium carbonate or sodium carbonate; the transition metal catalyst is  $\text{Pd}(\text{triphenyl-P})_4$ ; the oxidation is conducted with oxone; the non-reactive solvent is acetonitrile or tetrahydrofuran; the activating agent is  $\text{PBr}_3$  or  $\text{PCl}_5$  or  
 15         $\text{POCl}_3$  or  $(\text{PhO})_2\text{P}(\text{O})\text{Cl}$  or  $\text{MeSO}_2\text{Cl}$  or 4-MePh $\text{SO}_2\text{Cl}$  in the presence of a tri-C<sub>1</sub>-4alkylamine or  $(\text{CF}_3\text{SO}_2)_2\text{O}$  or  $(\text{FSO}_2)_2\text{O}$  in the presence of a tri-C<sub>1</sub>-4alkylamine; the polar organic solvent is N,N-dimethylformamide or tert-butyl alcohol; and the strong base is a sodium or potassium C<sub>1</sub>-4alkyloxide.

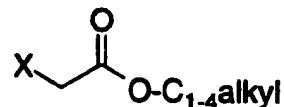
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9. A process of claim 8 wherein n is 0; X<sub>2</sub> is bromo or chloro; R<sub>1</sub> and R<sub>2</sub> are each independently selected from H or C<sub>1</sub>-4alkyl, and the coupling is conducted at 55 to 62°C, the reacting of compound B1  
 25        with activating agent is conducted at 0 to 25°C, and the reacting of compound A3 with strong base is conducted at 68 to 72°C.

10. A process according to claim 7 comprising the steps of

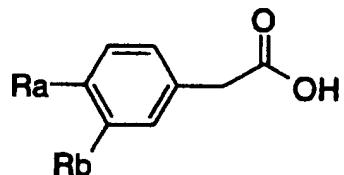
- 38 -

reacting a compound of Formula A1



A1

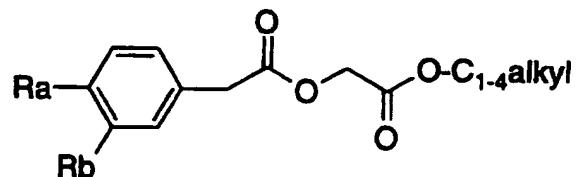
5 wherein X is chloride or bromo,  
in a non-reactive solvent and in the presence of a suitable base, with a  
compound of Formula A2



A2

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to yield a compound of Formula A3

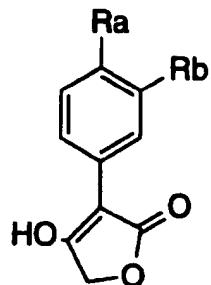


A3

15

reacting a compound of Formula A3  
in a polar organic solvent, in the presence of a strong base to yield a  
compound of Formula B1

- 39 -



B1

reacting a compound of Formula A3

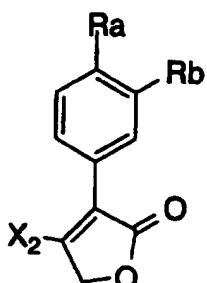
5 in a polar organic solvent, in the presence of a strong base to yield a compound of Formula B1



B1

10

reacting a compound of Formula B1 in a non-reactive solvent, with an activating agent to yield a compound of Formula C1

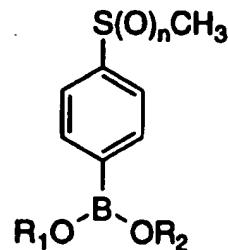


C1

15 wherein X2 is a good leaving group; and

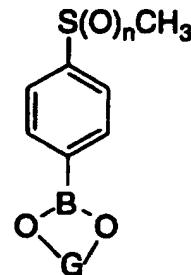
- 40 -

coupling a compound of Formula C1 with a compound of  
Formula D2

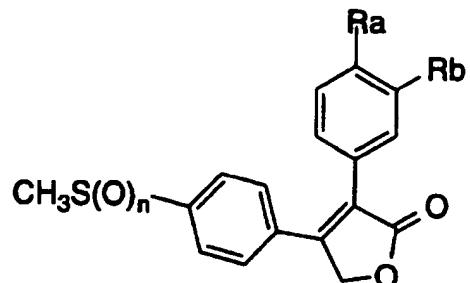


D2

5 wherein n is 0, 1 or 2;  
R<sub>1</sub> and R<sub>2</sub> are each independently selected from H or C<sub>1-4</sub>alkyl or R<sub>1</sub> and R<sub>2</sub> are joined, such that together with the atoms to which they are attached there is formed the compound of the formula



10 wherein G is a mono-cyclic saturated or unsaturated carbon ring of 5, 6 or 7 atoms,  
the coupling step being conducted in a coupling solvent in the presence of a coupling base and a transition metal catalyst to yield a compound of Formula D3



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- 41 -

D3

and where n is 0 or 1, oxidizing the compound of Formula D3 to a compound of Formula I.

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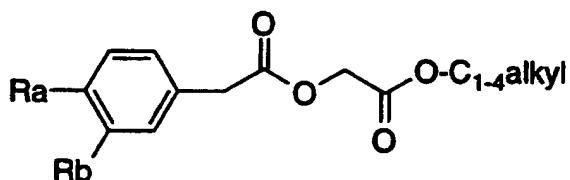
11. A process of claim 10 wherein the coupling solvent is toluene or diethoxymethane; the coupling base is potassium carbonate or sodium carbonate; the transition metal catalyst is  $Pd(triphenyl-P)_4$ ; the non-reactive solvent is acetonitrile or tetrahydrofuran; the activating agent is  $PBr_3$  or  $PCl_5$  or  $POCl_3$  or  $(PhO)_2P(O)Cl$  or  $MeSO_2Cl$  or 4-MePhSO<sub>2</sub>Cl in the presence of a tri-C<sub>1</sub>-4alkylamine or  $(CF_3SO_2)_2O$  or  $(FSO_2)_2O$  in the presence of a tri-C<sub>1</sub>-4alkylamine; the polar organic solvent is N,N-dimethylformamide or tert-butyl alcohol; and the strong base is a sodium or potassium C<sub>1</sub>-4alkyloxide.

15

12. A process of claim 11 wherein n is 0;  $X_2$  is bromo or chloro;  $R_1$  and  $R_2$  are each independently selected from H or C<sub>1</sub>-4alkyl, and the coupling is conducted at 55 to 62°C, the reacting of compound B1 with activating agent is conducted at 0 to 25°C, the reacting of compound A3 with strong base is conducted at 68 to 72°C, and the reacting of compound A1 with A2 is conducted at 0 to 25°C.

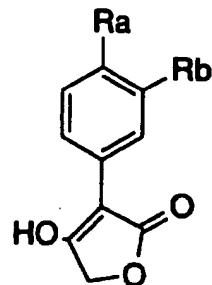
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13. A compound selected from the group consisting of



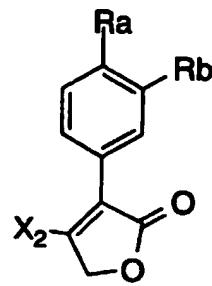
A3

- 42 -



B1

or



5

C1

wherein

X<sub>2</sub> is bromo or chloro; and

Ra and Rb are each independently selected from the group consisting of

10 (1) hydrogen, and  
(2) fluoro, bromo or chloro.

14. A compound according to Claim 12 wherein Ra and Rb are both hydrogen or are both fluoro.

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 95/11539A. CLASSIFICATION F SUBJECT MATTER  
IPC 6 C07D307/58 C07C69/614

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 C07D C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No. |
|------------|---|-----------------------|
| Y          | WO,A,94 15932 (G.D.SEARLE AND CO.) 21 July 1994<br>cited in the application<br>see the whole document, especially scheme IV, page 32 and example 13, page 61<br>--- | 1-14                  |
| P,A        | EP,A,0 623 606 (STERLING WINTHROP INC) 9 November 1994<br>see scheme II, page 6<br>---  | 1-14<br>-/-           |

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

## \* Special categories of cited documents :

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1

Date of the actual completion of the international search

5 January 1996

Date of mailing of the international search report

- 6. 02. 96

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Scruton-Evans, I

## INTERNATIONAL SEARCH REPORT

Int'l Application No  
PCT/US 95/11539

| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT |  | Relevant to claim No. |
|--|--|-----------------------|
| Category   | Citation of document, with indication, where appropriate, of the relevant passages   |                       |
| X  | J. CHEM. SOC., PERKIN TRANS. 1 (JCPRB4,0300922X);85; (8); PP.1567-76,<br>ORGANON LAB. LTD.;SCI. DEV. GROUP;<br>NEWHOUSE; ML1 5SH; UK (GB),<br>CAMPBELL A C ET AL 'Synthesis of (E)- and<br>(Z)-pulvinones'<br>see pages 1571 and 1572, preparations of<br>(11) and (12)<br>see page 1572, column 1, line 1-25<br>see the whole document<br>--- | 13,14                 |
| Y  |  | 1-14                  |
| A  | J. ORG. CHEM. (JOCEAH);67; VOL.32 (1);<br>PP.173-7, EASTMAN KODAK CO.;RES. LABS.;<br>ROCHESTER; N. Y.,<br>FORD J A, JR. ET AL 'The preparation of<br>2(5H)-furanones and dyes derived from<br>them'<br>---   | 1-14                  |
| A  | INDIAN JOURNAL OF CHEMISTRY,<br>vol. 29b, October 1990<br>pages 954-960,<br>D.K.DIKSHIT 'Synthesis and biological<br>activity of 2,3- and 3,4-diarylfurans and<br>2,3,4-triaryl-2,5-dihydrofurans'<br>see the whole document<br>-----  | 1-14                  |
| 1  |  |                       |

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International Application No

PCT/US 95/11539

| Patent document cited in search report | Publication date | Patent family member(s) |         | Publication date |
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|  |                  | JP-A-                   | 7025839 | 27-01-95         |
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